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GB 1318541 GB 1135689 GB 1128786

(58) Field of search
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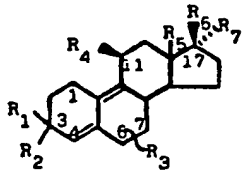
(54) 11β-substituted $\Delta^{4,9}$-steroids

(57) 11β-Substituted steroids of formula (I)



(I)

wherein

R_1 and R_2 are both hydrogen or, taken together, form the group oxo or $=CH_2$;

R_3 is an alkyl, alkenyl or alkynyl substituent at C-6 or C-7;

R_5 is alkyl;

R_6 is hydroxy and R_7 is hydrogen, alkyl, alkenyl or alkynyl, or

R_6 and R_7, taken together, form $=CH_2$;

R_4 is, e. g., an alkyl, cycloalkyl, phenyl or heterocyclic group, each optionally substituted by a substituent chosen from

(i) unsubstituted or substituted amino or heterocyclic amino,

(ii) a silyl group,

(iii) a hydroxy, alkoxy or aminoalkoxy group and

(iv) halogen or haloalkyl, and pharmaceutically or veterinarily acceptable salts thereof.

The compounds of formula (I) exhibit anti-progesterone and antiglucocorticoid activity and are useful in treatment of hormone-dependent tumors.

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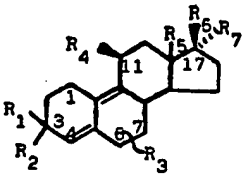
SPECIFICATION

11-β substituted steroids and process for their preparation

The present invention relates to new 11-β substituted steroids, to a process for their preparation and to pharmaceutical or veterinary compositions containing them.

The compounds of the invention have the following formula (I)



(I)

wherein

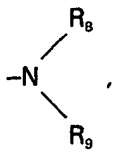
R_1 and R_2 are both hydrogen or R_1 and R_2, taken together, form the group oxo or the group $=CH_2$;

R_3 is a C–6 or C–7 substituent chosen from C_1–C_6 alkyl, C_2–C_5 alkenyl and C_2–C_5 alkynyl;

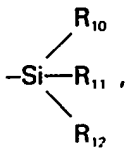
R_4 is a group $-(CH_2)_n-A-Z$, wherein n is zero or an integer of 1 to 3;

A is a bond or represents a C_4–C_7 cycloalkyl ring, a phenyl ring, or a saturated or unsaturated heteromonocyclic ring containing one or more heteroatoms chosen from O, S and N, and

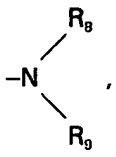
Z is (a) hydrogen, (b) a group



wherein each of R_8 and R_9 is, independently, hydrogen, C_1–C_6 alkyl or phenyl, or R_8 and R_9, taken together with the nitrogen atom to which they are linked, form a saturated heteromonocyclic ring containing one or more heteroatoms chosen from O, S and N; (c) a group



wherein each of R_{10}, R_{11} and R_{12}, which may be the same or different, is C_1–C_6 alkyl or phenyl; (d) a group $-O-(CH_2)_p-R_{13}$, wherein p is zero or an integer of 1 to 5 and R_{13} is hydrogen or a group



wherein R_8 and R_9 are as defined above; or (e) halogen or a halo-C_1–C_6 alkyl group;

R_5 is C_1–C_6 alkyl;

R_6 is hydroxy and R_7 is hydrogen, C_1–C_6 alkyl, C_2–C_5 alkenyl or C_2–C_5 alkynyl, or R_6 and R_7, taken together, form the group $=CH_2$.

The invention includes also the pharmaceutically or veterinarily acceptable salts of the compounds of formula (I), as well as all the possible isomers of formula (I) and their mixtures.

In this specification, the alkyl, alkenyl and alkynyl groups may be branched or straight chain.

A C_1–C_6 alkyl group is, preferably, C_1–C_3 alkyl, in particular methyl or ethyl.

A C_2–C_5 alkenyl group is, preferably, vinyl or allyl.

A C_2–C_5 alkynyl group is, preferably, ethynyl, 1-propynyl or 2-propynyl.

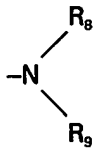
A halogen atom is, preferably, chlorine or fluorine, in particular fluorine.

A halo-C_1–C_6 alkyl group is, preferably, a di-halo- or tri-halo-C_1–C_6 alkyl group, in particular, difluoromethyl or trifluoromethyl.

When in the above given definition of R_4, A represents a C_4–C_7 cycloalkyl ring, this is.

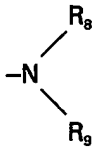
When A represents a saturated or unsaturated heteromonocyclic ring as reported above, it is, preferably, a piperidyl or pyridyl group.

In the case that A is a cycloalkyl or phenyl or heteromonocyclic ring as defined above with reference to formula (I), then Z indicates a substituent at any position of the said ring. When Z represents a group

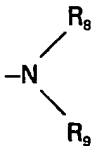


wherein each of R_8 and R_9 is, independently, C_1–C_6 alkyl, this is, preferably, C_1–C_4 alkyl, in particular methyl or ethyl.

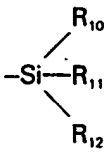
When Z represents a group



wherein R_8 and R_9, taken together with the nitrogen atom to which they are linked, form a heteromonocyclic ring as previously indicated, this is, preferably, piperazinyl, imidazolidinyl, morpholino or piperidino. The same applies to the definition of R_{13} when this represents a group



When Z represents a group

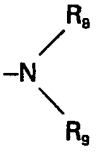


as defined above, preferably R_{10}, R_{11} and R_{12} are the same and represent a C_1–C_6 alkyl group, methyl in particular.

Preferably R_3 is a C_1–C_6 alkyl, in particular methyl or ethyl.

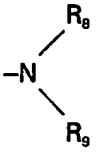
Preferably R_4 is a group $-(CH_2)_n-A-Z$, wherein either

1) n is 1, 2 or, most preferably 3, A is a bond and Z is a group

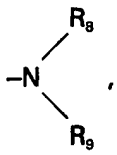


wherein R_8 and R_9 are as defined above; or

2) n is zero, A is phenyl, and Z is (i)

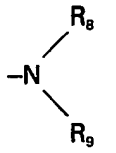


wherein R_8 and R_9 are as defined above, or (ii) $-O-(CH_2)_p-R_{13}$, wheren p is 1 or 2 and R_{13} is hydrogen or a group



wherein R_8 and R_9 are as defined above, or (iii) halogen or a halo-C_1–C_6 alkyl group.

Preferred



groups are amino and dimethylamino.

Preferred $-O-(CH_2)_p-R_{13}$ groups are methoxy, amino-ethoxy and dimethylamino-ethoxy.

Preferred halogen is fluorine and preferred halo-C_1–C_6 alkyl groups are difluoromethyl and, most particularly, trifluoromethyl.

Specific examples of preferred R_4 values are dimethylaminopropyl, dimethylamino-phenyl, dimethylamino-ethoxyphenyl, methoxy-phenyl, and trifluoromethyl-phenyl.

Preferably R_5 is methyl or ethyl, in particular methyl.

Preferably R_7 is C_1–C_6 alkyl or C_2–C_5 alkenyl or, most preferably, C_2–C_5 alkynyl, in particular 1-propynyl.

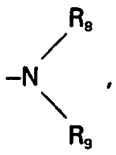
As already said, the invention includes also the pharmaceutically or veterinarily acceptable salts of the compounds of formula (I).

These salts may be the salts with either inorganic or organic pharmaceutically or veterinarily acceptable acids. Examples of inorganic acids are hydrochloric, hydrobromic, nitric, sulfuric and phosphoric acid; examples of organic acids are acetic, formic, propionic, benzoic, maleic, malic, fumaric, succinic, tartaric, citric, oxalic, methanesulfonic and ethanesulfonic acid.

In the above formula (I) and subsequent formulae a dashed line (IIIII) indicates a substituent in the α-configuration, i.e. below the plane of the ring; a wedged line (◀) indicates a substituent in the β-configuration, i.e. above the plane of the ring; a wavy line (~) indicates that a substituent may be in the α- or in the β-configuration or both.

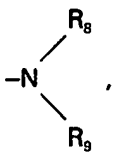
Consequently, where a formula has a substituent with a wavy line bond, the formula may represent a compound having the substituent solely in the α-configuration or solely in the β-configuration, or the formula may represent a mixture of both compounds having the substituent in the α-configuration and compounds having the substituent in the β-configuration.

A preferred class of compounds of the invention are the compounds of formula (I) wherein R_1 and R_2, taken together, form an oxo group; R_3 is C_1–C_6 alkyl; R_4 is a group $-(CH_2)_n-A-Z$ wherein n is an integer of 1 to 3, A is a bond and Z is a group

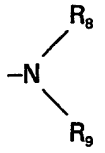


wherein each of R_8 and R_9 is, independently, hydrogen or C_1–C_6 alkyl; R_5 is C_1–C_2 alkyl; R_6 is hydroxy and R_7 is C_1–C_6 alkyl, C_2–C_5 alkenyl or C_2–C_5 alkynyl, and the pharmaceutically or veterinarily acceptable salts thereof.

Another preferred class of compounds of the invention are the compounds of formula (I) wherein R_1 and R_2, taken together, form a group oxo or $=CH_2$; R_3 is C_1–C_6 alkyl; R_4 is a group $-(CH_2)_n-A-Z$, wherein n is zero, A is phenyl and Z is (i)



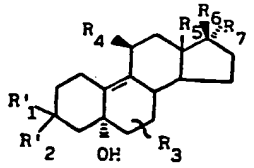
wherein each of R_8 and R_9 is, independently, hydrogen or C_1–C_6 alkyl, or (ii) $-O-(CH_2)_p-R_{13}$ wherein p is 1 or 2 and R_{13} is hydrogen or a group



wherein R_8 and R_9 are as defined above, or (iii) halogen or a halo-C_1–C_6-alkyl group; R_5 is C_1–C_2 alkyl; R_6 is hydroxy and R_7 is C_1–C_6 alkyl, C_2–C_5 alkenyl or C_2–C_5 alkynyl, and the pharmaceutically or veterinarily acceptable salts thereof.

Specific examples of preferred compounds of the invention are:
6β-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradien-3-one;
6β-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(3-N,N-dimethylaminopropyl)-4,5–9,10-estradien-3-one;
6β-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-trifluoromethylphenyl)-4,5–9,10-estradien-3-one;
6β-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-N,N-dimethylaminoethoxyphenyl)-4,5–9,10-estradien-3-one;
7α-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradien-3-one;
7α-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(3-N,N-dimethylaminopropyl)-4,5–9,10-estradien-3-one;
7α-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-trifluoromethylphenyl)-4,5–9,10-estradien-3-one;
7α-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-N,N-dimethylaminoethoxyphenyl)-4,5–9,10-estradien-3-one;
6β-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-methoxyphenyl)-4,5–9,10-estradien-3-one;
6β-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradien-3-one;
6β-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(3-N,N-dimethylaminopropyl)-4,5–9,10-estradien-3-one;
6β-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-trifluoromethylphenyl)-4,5–9,10-estradien-3-one;
6β-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-N,N-dimethylaminoethoxyphenyl)-4,5–9,10-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(3-N,N-dimethylaminopropyl)-4,5–9,10-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-trifluoromethylphenyl)-4,5–9,10-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-N,N-dimethylaminoethoxyphenyl)-4,5–9,10-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-methoxyphenyl)-4,5–9,10-estradien-3-one;
6β-methyl-3-methylene-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradiene;
7α-methyl-3-methylene-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradiene,
and, where appropriate, the pharmaceutically or veterinarily acceptable salts thereof.

The compounds of formula (I) are prepared by a process comprising dehydrating a compound of formula (II)



(II)

wherein

R_3, R_4, R_5, R_6 and R_7 are as defined above,

R'_1 and R'_2 are both hydrogen or, taken together, form a protected oxo group, or the group $=CH_2$, and, if desired, converting a compound of formula (I) into another compound of formula (I) and/or, if desired, converting a compound of formula (I) into a pharmaceutically or veterinarily acceptable salt thereof or obtaining a free compound from a salt, and/or, if desired, separating a mixture of isomers of formula (I) into the single isomers.

When in a compound of formula (II) R'_1 and R'_2, taken together, form a protected oxo group, the group oxo may be protected as acetal or thioacetal, e.g. dimethoxyacetal, diethoxyacetal, dimethylthioacetal or diethylthioacetal, or as ketal or thioketal, e.g. ethylenedioxyketal or ethylenedithioketal, most preferably as ethylenedioxyketal.

The dehydration of a compound of formula (II) may be carried out with a suitable dehydrating agent which may be, for example, a mineral, preferably concentrated, acid such as, for instance, hydrochloric or sulfuric acid, or also with a sulfonic resin.

The reaction may be performed in an inert, organic, preferably anhydrous, solvent such as, for

instance, methanol, ethanol, benzene, toluene, n-hexane or cyclohexane, at a temperature varying approximately between about 0°C and about 50°C, preferably at room temperature.

When the reaction is carried out on a compound of formula (II) wherein R'_1 and R'_2, taken together form a protected oxo group as defined above, deprotection proceeds at the same time with dehydration.

The optional conversion of a compound of formula (I) into another compound of formula (I) may be performed following known methods.

An optional conversion may be, for example, the conversion of a compound of formula (I) wherein R_1 and R_2, taken together, form a group oxo into the corresponding compound of formula (I) wherein R_1 and R_2 are both hydrogen: this transformation may be, e.g., carried out reacting first the 3-oxo-derivative (compound of formula (I) wherein R_1 and R_2, taken together, form oxo) with ethanedithiol in methanol and in the presence of boron trifluoride as catalyst, so obtaining the corresponding 3,3-ethylene-dithio-ketal, and, secondly, reducing the latter by known methods to obtain the corresponding compound of formula (I) wherein R_1 and R_2 are both hydrogen. In particular, for example, selective reduction may be obtained using the known methods described in the organic chemistry for reduction of thioketals; for instance, an alkali metal, such as e. g., Li, Na or K, in liquid ammonia according to, e.g., the procedure reported by R.E.Ireland et al in J. Amer. Chem. Soc. 1958, *80*, 4604, or Raney nickel according to, e.g., the procedure described by L.F.Fieser in J. Am. Chem. Soc. *70*, 1945, 1954, may be employed.

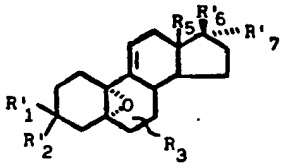
According to another optional conversion, a compound of formula (I) wherein R_1 and R_2, taken together, form an oxo group, may be transformed into the corresponding compound of formula (I) wherein R_1 and R_2, taken together, form the group $=CH_2$. This conversion may be, e.g., carried out by treatment with a Wittig reagent of formula $(\phi)_3P^{(+)}-CH_3 . Hal^{(-)}$ wherein ϕ is phenyl or a C_1–C_6 alkyl group and Hal is bromine or chlorine, following conventional procedures; for example, the reaction may be carried out using a slight excess of the Wittig reagent, operating in an inert organic solvent, such as, for instance, diethyl ether, tetrahydrofuran, n-hexane, dimethylsulfoxide, dimethylformamide or hexamethylphosphoramide, and in the presence of a base which may be, for example, sodium hydride or potassium tert-butoxide, at a temperature between about 0°C and the reflux temperature of the used solvent, preferably at room temperature.

Also the optional conversion of a compound of formula (I) into a salt thereof and the preparation of a free compound from a salt may be caried out according to known methods.

Conventional procedures, such as, e.g., fractional crystallization or chromathography, may be followed for separating a mixture of isomers into the single isomers.

A compound of formula (II) may be prepared by a process comprising:

1) reacting a compound of formula (III)



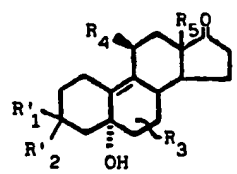
(III)

wherein

R'_1, R'_2, R_3 and R_5 are as defined above,

R'_6 is hydroxy and R'_7 is hydrogen, C_1–C_6 alkyl, C_2–C_5-alkenyl or C_2–C_5 alkynyl, with an organometallic compound, carrying the R_4 moiety, wherein R_4 is as defined above, so obtaining a compound of formula (II) wherein R_6 is hydroxy and R_7 is hydrogen, C_1–C_6 alkyl, C_2–C_5 alkenyl or C_2–C_5 alkynyl, and, if desired,

2) oxidizing a compound of formula (II) wherein R_6 is hydroxy and R_7 is hydrogen, so obtaining a compound of formula (IV)



(IV)

wherein

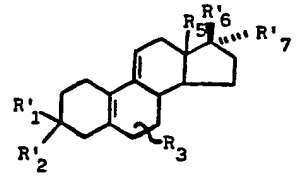
R'_1, R'_2, R_3, R_4 and R_5 are as defined above, and then

3) reacting a compound of formula (IV) with a Wittig reagent of formula $(\phi)_3P^{(+)}-CH_3 . Hal^{(-)}$ wherein ϕ and Hal are as defined above, so obtaining a compound of formula (II) wherein R_6 and

The organometallic compound carrying the R_4 moiety, used for the reaction with a compound of formula (III), may be, for example, $(R_4)_2CuLi$ or R_4Li or R_4MgX, wherein X is halogen, preferably chlorine, bromine or iodine.

The reaction is preferably carried out in the presence of a cuprous salt according to known methods, for example as described by G. Teutsh in Tetr.Lett. 22, 2021 (1979). The optional oxidation of a compound of formula (II) wherein R_6 is hydroxy and R_7 is hydrogen, to obtain a compound of formula (IV) may be performed according to known oxidation methods, for example with dicyclohexyl-carbodiimide and pyridine in the presence of trifluoroacetic acid at room temperature. For the reaction between a compound of formula (IV) and a Wittig reagent of formula $(\phi)_3P^{(+)}-CH_3.Hal^{(-)}$, conditions similar to those described above for the analogous reaction on a compound of formula (I) wherein R_1 and R_2 form an oxo group may be followed.

The compounds of formula (III) may be prepared by epoxidation of a compound of formula (V)



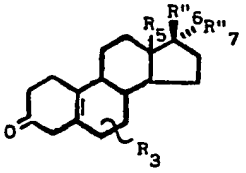
(V)

wherein

R'_1, R'_2, R_3, R_5, R'_6 and R'_7 are as defined above. The epoxidation reaction may be performed according to known methods, for example as reported by L. Nedelec in Bull. Soc. Chim. France 7, 2548, 1970.

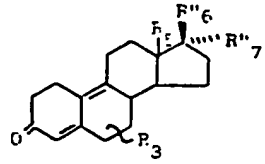
The compounds of formula (V) may be in their turn obtained by a multistep process comprising

1) bromination and dehydrobromination of a compound of formula (VI)



(VI)

wherein R_3 and R_5 are as defined above, R''_6 is a free or esterified hydroxy and R''_7 is hydrogen, so obtaining a compound of formula (VII)

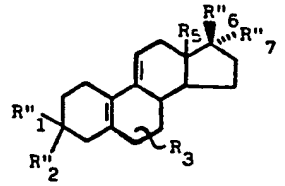


(VII)

wherein

R_3, R_5, R''_6 and R''_7 are as defined above;

2) protection of the free carbonyl group in a compound of formula (VII) so obtaining a compound of formula (VIII)



(VIII)

wherein

R_3, R_5, R''_6 and R''_7 are as defined above and

R''_1 and R''_2, taken together, form a protected oxo group; and

3) optional conversion of a compound of formula (VIII) into a compound of formula (V).

When R''_6 is an esterified hydroxy it may be, e.g., esterified with a C_2–C_7 aliphatic or aromatic carboxylic acid, such as, for instance, acetic acid or benzoic acid. The bromination and dehydrobromination of a compound of formula (VI) may be carried out by known methods, for example, by reaction with bromine, pyridine hydrobromide perbromide, or pyrrolidine hydrobromide per-

bromide in pyridine, and subsequent treatment with an appropriate base. The protection of the free carbonyl group in a compound of formula (VII) may be carried out according to known procedures; preferably protection by ketalization is carried out and conventional conditions are followed such as, for example, reaction with ethylene glycol, in the presence of catalytic amounts of *p*-toluene-sulfonic acid and, optionally, of ethyl orthoformate.

The optional conversion of a compound of formula (VIII) into a compound of formula (V) includes, e.g., the following transformations which may be carried out in any preferred order:

a) saponification of a compound of formula (VIII) wherein R''_6 is an esterified hydroxy so obtaining a compound of formula (V) wherein R'_6 is free hydroxy, R'_7 is hydrogen and R'_1 and R'_2, taken together, form a protected oxo group;

b) oxidation of a compound (V) obtained under a) above to give the corresponding 17-oxo-derivative followed by nucleophilic addition to the 17-oxo group with an organometallic reagent carrying a R'''_7 moiety, where R'''_7 is C_1–C_8 alkyl, C_2–C_5 alkenyl or C_2–C_5 alkynyl, so obtaining a compound of formula (V) wherein R'_6 is free hydroxy and R'_7 is C_1–C_6 alkyl, C_2–C_5 alkenyl or C_2–C_5 alkynyl, and R'_1 and R'_2, taken together, form a protected oxo group;

c) reduction at the protected oxo group represented by R''_1 and R''_2, or by R'_1 and R'_2, so obtaining a compound of formula (V) wherein R'_1 and R'_2 are both hydrogen; or

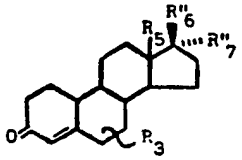
d) deprotection of the oxo group represented by R''_1 and R''_2, or by R'_1 and R'_2, and Wittig reaction with a compound of formula $(\phi)_3P^{(+)}–CH_3 . Hal^{(-)}$, wherein ϕ and Hal are as defined above, so obtaining a compound of formula (V) wherein R'_1 and R'_2, taken together, form the group $=CH_2$.

The transformations indicated above may be performed according to known methods following conventional procedures.

In particular, for example, the saponification reaction a) may be e.g. carried out with an alkali metal e.g. lithium, sodium or potassium, hydroxide in an alcoholic, e.g. methanolic, medium according to known methods, while for the reactions indicated under b), c) and d) conditions similar to those previously described in this specification for analogous reactions may be followed.

In particular, for instance, the oxidation of a compound of formula (V) wherein R'_6 is free hydroxy and R'_7 is hydrogen to give the corresponding 17-oxo-derivative, may be carried out in analogous way as described above for the preparation of a compound of formula (IV). Similarly, the nucleophilic addition on said 17-oxo group may be, e.g., performed with an organometallic reagent of formula $(R'''_7)_2CuLi$ or R'''_7Li or R'''_7MgX where R'''_7 and Mg are as defined above, operating in analogous way as reported above for the reaction between a compound of formula (III) and the analogous organometallic compounds.

The compounds of formula (VI) may be obtained through protection, e.g., by ketalization as reported above, of a compound of formula (IX)

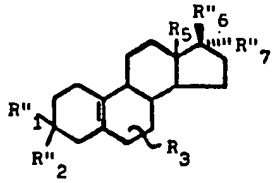


(IX)

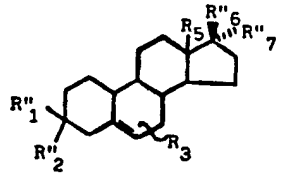
wherein

R_3, R_5, R''_6 and R''_7 are as defined above.

A mixture of Δ5(10) and Δ5(6) isomers of formula (Xa) and, respectively, (Xb)



(Xa)



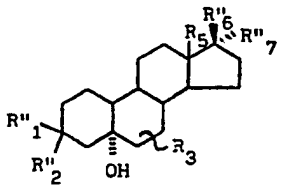
(Xb)

wherein

R''_1, R''_2, R_3, R_5, R''_6 and R''_7 are as defined above, is obtained.

The Δ5(10) isomer is separated from the mixture, e.g. by fractional crystallization or chromatography, and then deprotected at the oxo group in a conventional way.

In alternative, the compounds of formula (VI) may also be obtained by dehydrating a compound of formula (XI)



(XI)

wherein

R''_1, R''_2, R_3, R_5, R''_6 and R''_7 are as defined above, and then removing the protecting group of the oxo function.

Dehydration may be, e.g., carried out with a dehydrating agent chosen from $SOCl_2$, P_2O_5 and dicyclohexylcarbodiimide operating in an inert anhydrous solvent such as, for instance, pyridine, tetrahydrofuran, methylenechloride or benzene.

The removal of the protecting group of the oxo function may be performed conventionally, preferably under mild conditions, e.g. with acetic or formic or oxalic acid in aqueous acetone.

The compounds of formula (IX) are known [R. Villotti, J. Am. Chem. Soc. 81, 4566 (1959) and J.F. Grunwell, Steroids 27, *6*, 759 (1965)] or may be prepared by known methods.

Also the compounds of formula (XI) are known compounds or may be prepared following known procedures from known compounds.

The compounds of the invention show antiprogesterone and antigluccorticoid activity.

Though *in vitro* the compounds of the invention were found to have affinity for the progesterone receptors of rabbit uterus and for the glucocorticoid receptors of rat thymus, however, after *in vivo* administration, they were found to be progesterone antagonists and glucocorticoid antagonists without any agonistic effect.

The progestomimetic and antiprogestomimetic activities were evaluated in rabbit by measuring the proliferation of the uterine mucosa according to Mc Phail (J.Physiol. *83*, 145, 1934). The compounds were administered for four consecutive days at various doses, alone and together with a standard dose of progesterone.

The glucocorticoid and antiglucocorticoid activities were evaluated in the liver glycogen accumulation test in rats according to G.P.Guthrie (Endocrinology *107*, 1393, 1980). Rats, fasted for 14 hours, were treated with various doses of the compounds alone (glucocorticoid activity) and together with a standard dose of the glucocorticoid dexamethasone (antiglucocorticoid activity), and liver glycogen was estimated in animals killed after 7 hours.

Progesterone is a key hormone in the establishment and maintenance of human pregnancy and is involved in several hormone-dependent tumors. In view of their antiprogesterone activity the compounds of the present invention can therefore be useful in inducing menstruation when administered in the luteal phase of the menstrual cycle, in preventing implantation when administered at nidation, and in inducing abortion when administered early in pregnancy.

Furthermore the compounds of the invention may be useful in the control of hormonal imbalances and as antitumor agents for the treatment of hormone-dependent tumors such as, e.g., breast cancer and endometrial cancer.

Owing to their antiglucocorticoid activity the compounds of the invention are also useful for treating, e.g., glucocorticoid hypersecretion, ageing in general, and hypertension.

The compounds of the invention can be administered in any suitable way, for instance orally, parenterally, e.g. by intravenous injection or infusion or by intramuscular injection, intravaginally, or topically.

Oral administration is particularly appropriate for the compounds of the invention because the presence of the C_6 or C_7 R_3 substituent in the compounds of formula (I) results in enhanced activity by oral route.

The dosages are strongly dependent on the weight, age, conditions and case history of the patient to be treated.

For the oral administration the dosage range may be, for example, between 10 mg and 400 mg one or more times a day for some days.

The pharmaceutical compositions of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

For example, the solid oral forms, e.g. tablets and capsules, may contain, together with the active compound, diluents, e.g., lactose, dextrose, saccharose, cellulose, corn starch and potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethyl cellulose, polyvinylpyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, for instance, lecithin, polysorbates, layrylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations.

Said pharmaceutical preparations may be manufactured in known manner, for example, by

means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

The liquid dispersions for oral administration may be, e.g., syrups, emulsions and suspensions.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol; in particular a syrup to be administered to diabetic patients can contain as carriers only products not metabolizable to glucose, or metabolizable in very small amount to glucose such as, sorbitol. The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injections or infusions may contain as carrier, for example, a sterile water or, preferably, they may be in the form of sterile aqueous isotonic saline solutions.

The vaginal tablets may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. cocoa-butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

Compositions for topical application such as, e.g., creams, lotions or pastes, may be, e.g., prepared by admixing the active ingredient, with a conventional oleaginous or emulsifying excipient.

This invention is illustrated but not limited by the following examples wherein the abbreviations THF, DMSO and TLC stand, respectively, for tetrahydrofuran, dimethylsulfoxide, and "thin layer chromatography".

Example 1

A slurry of 19-nor-5α-hydroxy-6β-methyl-3-oxo-17β-hydroxy androstane-3,3-ethylenedioxy-17-acetate (12,69g) in 190 ml of pyridine was cooled with external bath and then, under stirring, 12.7 ml of $SOCl_2$ were dropped into the vessel and the temperature was maintained below 5°C. When the addition was completed, the mixture was stirred for 10 minutes then water (200 ml) was added and the aqueous layer was extracted some times with ethylacetate. The organic phase was washed with water, dried over Na_2SO_4 and the solvent was removed to yield 14.2 g of crude 6β-methyl-17β-hydroxy-5,10-estren-3-one-3,3-ethylenedioxy-17-acetate [NMR ($CDCl_3$)δ: 0.81 (3H,s); 1.05 (3H,d); 2.03 (3H,s); 3.98 (4H,s); 4.66 (1H,dd)].

The crude product was dissolved in (130ml) of diethylether and the solution was treated with 640 ml of 65% aqueous acetic acid and stirred 24 hours at room temperature (20°C).

The reaction mixture was diluted with 1,3 l of water and extracted several times with ethylacetate.

The organic phase was dried, the solvent was removed in vacuum and acetic acid was distilled in azeotropic mixture with cyclohexane. The crude was purified on silica gel using diethylether:n-hexane 1:1 as eluant to give 7.85 g of pure oily 6β-methyl-17β-hydroxy-5,10-estren-3-one-17-acetate [NMR ($CDCl_3$) δ :0.84 (3H,s,C_{18}); 1.04 (3H,d,C_6); 2.04 (3H,s); 2.63 (1H,d,C_4); 2.98 (1H,d,C_4); 4.65 (1H, dd,C_{17})].

Using the same method the following compounds were prepared:
6β-ethyl-17β-hydroxy-5,10-estren-3-one-17-acetate;
6β-n-propyl-17β-hydroxy-5,10-estren-3-one-17-acetate;
6β-isopropyl-17β-hydroxy-5,10-estren-3-one-17-acetate.

When 6β-methyl-17β-hydroxy-5,10-estren-3-one-17-acetate (7.15 g) was dissolved into 500 ml of dry benzene and 50 g of basic Al_2O_3 were added, the mixture was warmed to reflux for 1 hour, the Al_2O_3 was filtered and the solvent was removed, then crude 6α-methyl-17β-hydroxy-5,10-estren-3-one-17-acetate (7.1 g) was obtained; chromatographic purification on silica gel using ethyl acetate: n-hexane 1:1 yielded 4 g of pure 6α-methyl-17β-hydroxy-5,10-estren-3-one-17-acetate (oil).

Example 2

To a solution of 6β-methyl-17β-hydroxy-5,10-estren-3-one-17-acetate(7.85g) in 380 ml of dry pyridine, operating in atmosphere of dry nitrogen and cooling with external bath, 9.9g of pyridinium hydrobromide perbromide were added portionwise. The mixture was stirred for 15 minutes then warmed at 50°C and stirred 1 hour.

The reaction mixture was quenched in 500 ml of water, acidified to pH 2 with 98% H_2SO_4 and extracted with ethylacetate. The organic phase was dried then the solvent was removed in vacuum and the crude 6β-methyl-17β-hydroxy-4,5–9,10-estradien-3-one-17-acetate was chromatographed on silica gel using diethyl ether:n-hexane-6:4 thus obtaining 6.12 g of pure 6β-methyl-17β-hydroxy-4,5–9,10-estradien-3-one-17-acetate as white crystals, m.p. 97–99°C, UV (EtOH) λmax=304, ε=19,429; $[\alpha]_D$=−215° (C=1,$CHCl_3$); NMR ($CDCl_3$)δ: 0.92 (3H,s); 1.04 (3H,d); 2.02 (3H,s); 4.64 (1H,dd); 5.70 (1H,s).

6β-ethyl-17β-hydroxy-4,5–9,10-estradien-3-one-17-acetate;
6α-methyl-17β-hydroxy-4,5–9,10-estradien-3-one-17-acetate;
7α-methyl-17β-hydroxy-4,5–9,10-estradien-3-one-17-acetate;
7α-ethyl-17β-hydroxy-4,5–9,10-estradien-3-one-17-acetate.

Example 3

To a solution of 6β-methyl-17β-hydroxy-4,5–9,10-estradien-3-one-17-acetate(9.2 g) in 100 ml of dry CH_2Cl_2, 6.3 ml of ethylene glycol, 7.5 ml of ethyl orthoformate and 0.24 g of p-toluenesulphonic acid were added, then the mixture was warmed at 40°C and stirred for 1.5 hours.

The reaction mixture was neutralized with triethylamine, diluted with 100 ml of ethyl acetate and washed with saturated potassium carbonate solution, dried; the solvent was then removed to yield 10 g of crude 6β-methyl-17β-hydroxy-5-,10–9,11-estradien-3-one-3,3-ethylenedioxy-17-acetate.

The crude product was dissolved into 150 ml of methanol and treated with 6 g of lithium hydroxide and 50 ml of water.

The solution was stirred 1.5 hours at room temperature then was neutralized with 2N HCl; the methanol was distilled off and the residue was extracted with ethylacetate.

The organic phase was dried and evaporated in vacuum to yield 9.7 g of 6β-methyl-17β-hydroxy-5,10–9,11-estradien-3-one-3,3-ethylenedioxy. To a solution of 6.44 g of the crude 6β-methyl-17β-hydroxy-5,10–9,11-estradien-3-one-3,3-ethylenedioxy, in 60 ml of dry DMSO/benzene 1/1 mixture, 12.1 g of dicyclohexylcarbodiimide, 1.57 ml of pyridine and 0.77 ml of trifluoroacetic acid were added and then the mixture was stirred at 20°C for 5 hours. When oxidation was completed (TLC monitoring) the mixture was diluted with 90 ml of benzene, the solid was filtered by suction and the organic phase was evaporated in vacuum. The obtained crude was chromatographed on silica gel (diethyl ether:n-hexane:triethylamine 50:50:0.2 as eluant) to yield 5.74 g of pure 6β-methyl-5,10–9,11-estradien-3,3-ethylenedioxy-3,17-dione, $[\alpha]_D = +267°$ (C=1, $CHCl_3$); NMR ($CDCl_3$)δ: 0.88 (3H,s); 1.12 (3H, d); 3.98 (4H,s); 5.56 (1H,m).

Following analogous procedure the below listed compounds were prepared:
6β-ethyl-5,10–9,11-estradien-3,3-ethylenedioxy-3,17-dione;
6β-propyl-5,10–9,11-estradien-3,3-ethylenedioxy-3,17-dione;
6α-methyl-5,10–9,11-estradien-3,3-ethylenedioxy-3,17-dione;
6α-ethyl-5,10–9,11-estradien-3,3-ethylenedioxy-3,17-dione;
7α-methyl-5,10–9,11-estradien-3,3-ethylenedioxy-3,17-dione;
7α-ethyl-5,10–9,11-estradien-3,3-ethylenedioxy-3,17-dione.

Example 4

Into a 2.2 M solution of ethylmagnesium bromide in dry THF (120 ml) methylacetylene dried on calcium chloride was bubbled for two hours, cooling at 30°C with external termostatic bath. Then, under dry argon atmosphere, a solution of 8.6 g of 6β-methyl-5,10–9,11-estradien-3,3-ethylenedioxy-3,17-dione in 35 ml of dry THF was dropped into the mixture. The reaction mixtute was stirred for 1 hour then was quenched in 500 ml of ice-water/NH_4Cl mixture and extracted several times with diethyl ether.

The organic phase was washed with water, dried, and the solvent was removed; the crude residue was purified on Al_2O_3 using ethyl acetate:n-hexane 10:90 as eluant to yield 8.7 g of pure 6β-methyl-17β-hydroxy-17α-(1-propynyl)-3,3-ethylenedioxy-5,10–9,11-estradien-3-one, $[\alpha]_D = +161°$ (C=1, $CHCl_3$); NMR ($CDCl_3$)δ: 0.84 (3H,s); 1.09 (3H,d); 1.83 (3H,s); 3.98 (4H,s); 5.55 (1H,m).

Following analogous procedure the herebelow reported compounds were prepared:
6β-ethyl-17β-hydroxy-17α-(1-propynyl)-3,3-ethylenedioxy-5,10–9,11-estradien-3-one;
6β-propyl-17β-hydroxy-17α-(1-propynyl)-3,3-ethylenedioxy-5,10–9,11-estradien-3-one;
6α-methyl-17β-hydroxy-17α-(1-propynyl)-3,3-ethylenedioxy-5,10–9,11-estradien-3-one;
6α-ethyl-17β-hydroxy-17α-(1-propynyl)-3,3-ethylenedioxy-5,10–9,11-estradien-3-one;
7α-methyl-17β-hydroxy-17α-(1-propynyl)-3,3-ethylenedioxy-5,10–9,11-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-(1-propynyl)-3,3-ethylenedioxy-5,10–9,11-estradien-3-one.

Following analogous procedure but using acetylene instead of methylacetylene, the corresponding ethynyl compounds listed below were prepared:
6β-methyl-17β-hydroxy-17α-ethynyl-3,3-ethylenedioxy-5,10–9,11-estradien-3-one;
6β-ethyl-17β-hydroxy-17α-ethynyl-3,3-ethylenedioxy-5,10–9,11-estradien-3-one;
6β-propyl-17β-hydroxy-17α-ethynyl-3,3-ethylenedioxy-5,10–9,11-estradien-3-one;
6α-methyl-17β-hydroxy-17α-ethynyl-3,3-ethylenedioxy-5,10–9,11-estradien-3-one;
6α-ethyl-17β-hydroxy-17α-ethynyl-3,3-ethylenedioxy-5,10–9,11-estradien-3-one;
7α-methyl-17β-hydroxy-17α-ethynyl-3,3-ethylenedioxy-5,10–9,11-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-ethynyl-3,3-ethylenedioxy-5,10–9,11-estradien-3-one.

Example 5

A solution of 6β-methyl-17β-hydroxy-17α-(1-propynyl)-3,3-ethylenedioxy-5,10–9,11-estradien-3-one (7.78 g) in 100 ml of CH_2Cl_2, cooled to −5° to −10°C, was treated portionwise with 4.78 g of *m*-chloroperbenzoic acid, and stirred for 45 minutes; then, under stirring, 4.62 g of K_2CO_3 were added and the slurry was left to rise to room temperature in 30 minutes.

The solid was filtered and the organic phase was diluted with ethyl acetate and washed with 5% $NaHCO_3$ aqueous solution, then dried, and the solvent was removed.

The crude product was chromatographed on silica gel using n-hexane:ethyl acetate:triethylamine 70:30:0.2 as eluant to yield 3.85 g of 6β-methyl-5,10-α-epoxide-17β-hydroxy-17α-(1-propynyl)-3,3-ethylenedioxy-9,11-estren-3-one,$[\alpha]_D = -1.1°$ (C=1, $CHCl_3$), NMR ($CDCl_3$)δ: 0.83 (3H,s); 1.14 (3H,d); 1.85 (3H,s); 3.92 (4H,m); 6.04 (1H,m).

Using analogous procedure, the 5,10-α-epoxide derivatives of the compounds listed in example 4 were prepared.

Example 6

A 1M solution of *p*-dimethylamino-phenyl-magnesium bromide in THF (240 ml) was cooled to −30°C under dry nitrogen atmosphere and then 1.20 g of CuCl were added. The mixture was stirred for 20 minutes and then, cooling at −30°C with external bath, a solution of 15 g of 6β-methyl-5,10-α-epoxide-17β-hydroxy-17α-(1-propynyl)-3,3-ethylenedioxy-9,11-estren-3-one in 80 ml of THF was added dropwise.

The temperature was kept for 1 hour at −30°C, then left to rise to room temperature. The mixture was quenched with 500 ml of iced NH_4Cl solution and extracted with ethyl acetate; the organic phase was washed with saturated NaCl aqueous solution, dried, and the solvent was removed. The crude was purified on silica gel column using n-hexane:ethyl acetate:triethylamine 60:40:0.2 as eluant to give 14.1 g of 6β-methyl-5α-17β-dihydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-3,3-ethylenedioxy-9,10-estren-3-one, $[\alpha]_D = -13°$ (C=1,$CHCl_3$); NMR ($CDCl_3$)δ:0.44 (3H,s); 1.05 (3H,d); 1.96 (3H,s); 2.90 (6H,s); 4.00 (4H,m); 4.16 (1H,m); 6.70 (2H,d); 7.10 (2H,d).

Example 7

To a cooled 1M solution 3-(N,N'-dimethylamino)-propyl magnesium bromide in THF (80 ml) 8.40 g of dimethyl sulfide-CuBr complex, dissolved in 40 ml of THF, were added under dry nitrogen atmosphere.

The mixture was stirred for 15 minutes at 0°C, then a solution of 6β-methyl-5,10-α-epoxide-17β-hydroxy-17α-(1-propynyl)-3,3-ethylenedioxy-9,11-estren-3-one (5 g) in 25 ml of THF was added dropwise.

The reaction mixture was stirred for 2 hours at 0°C then was left to rise to room temperature and was quenched with 200 ml of iced 20% ammonium chloride solution.

The solution was extracted with ethyl acetate, the organic phase was washed with saturated sodium chloride aqueous solution, then dried and the solvent distilled at reduced pressure to yield a crude product. This was chromatographed on silica gel and eluted with cyclohexane:ethyl acetate: triethylamine 50:50:0.2 to give 3.4 g of 6β-methyl-5α,17β-dihydroxy-17α-(1-propynyl)-11β-(3-N,N-dimethylaminopropyl)-3,3-ethylenedioxy-9,10-estren-3-one, NMR ($CDCl_3$)δ:0.45 (3H,s); 1.05 (3H,d); 1.90 (3H,s); 2.25 (6H,s); 4.00 (4H,m); 4.15 (1H,m).

Example 8

In an inert atmosphere of dry argon a 1M solution of p-trifluoromethyl-phenyl-magnesium bromide in THF (40 ml) was cooled to −25°C and then 0.22 g of CuCl were added. The mixture was stirred for 10 minutes then a solution of 6β-methyl-5,10-α-epoxide-17β-hydroxy-17α-(1-propynyl)-3,3-ethylenedioxy-9,11-estren-3-one (2.5 g) in 20 ml of dry THF was dropped, while the temperature was maintained at −25°C. The solution was stirred 90 minutes, then the reaction mixture was quenched with 100 ml of 5% aqueous solution of NH_4Cl and ice. The mixture was extracted with diethyl ether and the organic phase was washed with saturated saline solution and dried. The solvent was removed at reduced pressure and the residue was purified by silica gel chromatography using methylene chloride:methanol 90:10 as eluant to yield 1.8 g of 6β-methyl-5α-17β-dihydroxy-17α-(1-propynyl)-11β-(4-trifluoromethylphenyl)-3,3-ethylenedioxy-9,10-estren-3-one, NMR ($CDCl_3$)δ: 0.45 (3H,s); 1.04 (3H,d); 1.96 (3H,s); 4.00 (4H,m);4.15 (1H,m); 6.71 (2H,d); 7.10 (2H, d).

Example 9

To a solution of dimethyl sulfide CuBr complex (4.2 g) in 15 ml of dry THF, 40 ml of a 1M solution of 4-(N,N-dimethylamino-ethoxy)-phenyl magnesium bromide in THF were added dropwise under dry nitrogen atmosphere while maintaining the reaction temperature at 0°C with external cooling bath. After 30 minutes stirring a solution of 6β-methyl-5,10α-epoxide-17β-

dropped. The reaction mixture was stirred 1 hour at 0°C then was quenched into 100 ml of 5% iced ammonium chloride solution. The solution was extracted with diethyl ether, and the organic layer was washed with saline solution, and dried. The ether was then removed to give a crude product that was purified on silica gel with n-hexane:ethyl acetate:triethylamine 60:40:0.1 as eluant phase to give pure 6β-methyl-5α,17β-dihydroxy-17α-(1-propynyl)-11β-(4-N,N-dimethylaminoethoxy-phenyl)-3,3-ethylenedioxy-9,10-estren-3-one (1.75 g), NMR ($CDCl_3$)δ: 0.46 (3H,s); 1.05 (3H,d); 1.95 (3H,s); 2.38 (6H,s); 4.00 (4H,m); 6.75 (2H,d); 7.10 (2H,d).

Example 10

To a solution of 6β-methyl-5α,17β-dihydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-3,3-ethylenedioxy-9,10-estren-3-one (11.3 g) in 400 ml of methanol, 14 ml of concentrated hydrochloric acid were added and the solution was stirred at 25°C for 30 minutes.

In this time the deketalization was completed and the reaction mixture was diluted with 1000ml of diethyl ether and neutralized with 350 ml of 1N sodium hydroxide aqueous solution. The organic phase was separated and the aqueous layer was extracted with diethyl ether.

The combined organic extracts were washed with NaCl aqueous solution, dried and the ether was removed. The residue was purified on silica gel column with a mixture of n-hexane:ethyl acetate 50:50 as eluant to give 9.2 g of pure 6β-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradien-3-one, $[\alpha]_D = +149.5°$ (C=1,$CHCl_3$); UV (EtOH) λmax=262, ε=17,764; λmax=306, ε=19,403; NMR ($CDCl_3$)δ: 0.55 (3H,s); 1.28 (3H,d); 1.87 (3H,s); 2.88 (6H,s); 4.36 (1H,m); 5.80 (1H,s); 6.68 (2H,d); 7.04 (2H,d).

Example 11

Using the procedure described in example 10, starting from appropriate intermediates prepared according to the examples 6, 7, 8 and 9, the following compounds were obtained:
6α-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradien-3-one;
6β-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(3-N,N-dimethylaminopropyl)-4,5–9,10-estradien-3-one;
6β-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-trifluoromethylphenyl)-4,5–9,10-estradien-3-one;
6β-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-N,N-dimethylaminoethoxyphenyl)-4,5–9,10-estradien-3-one;
7α-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradien-3-one;
7α-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(3-N,N-dimethylaminopropyl)-4,5–9,10-estradien-3-one;
7α-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-trifluoromethylphenyl)-4,5–9,10-estradien-3-one;
7α-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-N,N-dimethylaminoethoxyphenyl)-4,5–9,10-estradien-3-one;
6β-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-methoxyphenyl)-4,5–9,10-estradien-3-one;
6β-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradien-3-one;
6β-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(3-N,N-dimethylaminopropyl)-4,5–9,10-estradien-3-one;
6β-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-trifluoromethylphenyl)-4,5–9,10-estradien-3-one;
6β-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-N,N-dimethylaminoethoxyphenyl)-4,5–9,10-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(3-N,N-dimethylaminopropyl)-4,5–9,10-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-trifluoromethylphenyl)-4,5–9,10-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-N,N-dimethylaminoethoxyphenyl)-4,5–9,10-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-methoxyphenyl)-4,5–9,10-estradien-3-one;
6β-methyl-17β-hydroxy-17α-ethynyl-11β-(4-dimethylaminophenyl)-4,5–9,10-estradien-3-one;
6β-methyl-17β-hydroxy-17α-ethynyl-11β-(3-N,N-dimethylaminopropyl-4,5–9,10-estradien-3-one;
6β-methyl-17β-hydroxy-17α-ethynyl-11β-(4-trifluoromethylphenyl)-4,5–9,10-estradien-3-one;
6β-methyl-17β-hydroxy-17α-ethynyl-11β-(4-N,N-dimethylaminoethoxyphenyl)-4,5–9,10-estradien-3-one;
7α-methyl-17β-hydroxy-17α-ethynyl-11β-(4-dimethylaminophenyl)-4,5–9,10-estradien-3-one;
7α-methyl-17β-hydroxy-17α-ethynyl-11β-(3-N,N-dimethylaminopropyl)-4,5–9,10-estradien-3-one;
7α-methyl-17β-hydroxy-17α-ethynyl-11β-(4-trifluoromethylphenyl)-4,5–9,10-estradien-3-one;
7α-methyl-17β-hydroxy-17α-ethynyl-11β-(4-N,N-dimethylaminoethoxyphenyl)-4,5–9,10-estradien-3-one;
6β-methyl-17β-hydroxy-17α-ethynyl-11β-(4-methoxyphenyl)-4,5–9,10-estradien-3-one;
6β-ethyl-17β-hydroxy-17α-ethynyl-11β-(4-dimethylaminophenyl)-4,5–9,10-estradien-3-one;
6β-ethyl-17β-hydroxy-17α-ethynyl-11β-(3-N,N-dimethylaminopropyl)-4,5–9,10-estradien-3-one;
6β-ethyl-17β-hydroxy-17α-ethynyl-11β-(4-trifluoromethylphenyl)-4,5–9,10-estradien-3-one;
6β-ethyl-17β-hydroxy-17α-ethynyl-11β-(4-N,N-dimethylaminoethoxyphenyl)-4,5–9,10-estradien-3-one;

7α-ethyl-17β-hydroxy-17α-ethynyl-11β-(4-dimethylaminophenyl)-4,5–9,10-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-ethynyl-11β-(3-N,N-dimethylaminopropyl)-4,5–9,10-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-ethynyl-11β-(4-trifluoromethylphenyl)-4,5–9,10-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-ethynyl-11β-(4-N,N-dimethylaminoethoxyphenyl)-4,5–9,10-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-ethynyl-11β-(4-methoxyphenyl)-4,5–9,10-estradien-3-one.

Example 12

To a solution of 6α-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradien-3-one (1.12 g) in 4 ml of dimethylsulfoxide, 7 ml of the ylide prepared with 2.3 g of triphenylphosphonium iodide and 0.52 of potassium tert-butoxide in 10 ml of dimethylsulfoxide, were added dropwise. The solution was stirred in inert atmosphere for 4 hours at room temperature then was quenched with ammonium chloride solution and extracted with diethyl ether. The solvent was removed and the crude product was purified on silica gel with n-hexane:ethyl acetate 85:15 as eluant to yield 0.68 g of pure 6α-methyl-3-methylene-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradiene.

In the same way the 3-methylene derivatives of the comounds reported in example 11 were prepared, in particular: 6β-methyl-3-methylene-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradiene; and 7α-methyl-3-methylene-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradiene.

Example 13

A solution of 6β-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradien-3-one (2.35 g) in methanol (25 ml) was reacted with ethane-1,2-dithiol (1 ml) and borontrifluoride (0.7 g).

The mixture was stirred for 1 hour at room temperature and then evaporated to yield the 3-thioketal.

To a suspension of the crude 6β-methyl-3-oxo-3,3-ethylenethioketal-4,5–9,10-estradiene (2.4 g) in 20 ml of dry diethyl ether and 50 ml of liquid ammonia 0.5 g of sodium metal were added; ethanol was then added until the blue colouration was dispelled and the ammonia was evaporated.

The residue was treated with 50 ml of 5% ammonium chloride aqueous solution and then extracted with diethyl ether.

Purification on silica gel column with n-hexane:ethyl acetate 80:20 as eluant yielded 1.35 g of pure 6β-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradiene.

Following analogous procedure the 3-deoxo-estradiene derivatives of the estradien-3-one compounds listed in example 11 were prepared, in particular:
7α-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradiene.

Example 14

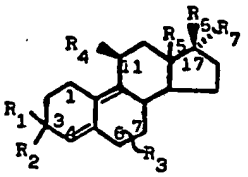
Tablets each weighing 0.120 g and containing 50 mg of the active substance, were manufactured as follows:

Composition (for 10,000 tablets)	
6β-methyl-17β-hydroxy-17α-(1-propynyl)--11β-(4-dimethylamino-phenyl)-4,5–9,10--estradien-3-one	500 g
Lactose	500 g
Corn starch	180 g
Talc powder	15 g
Magnesium stearate	5 g

The 6β-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylamino-phenyl)-4,5–9,10-estradien-3-one, the lactose and half the corn starch were mixed; the mixture was then forced through a sieve of 0.5 mm mesh size. Corn starch (10 g) was suspended in warm water (90 ml) and the resulting paste was used to granulate the powder. The granulate was dried, comminuted on a sieve of 1.4 mm mesh size, then the remaining quantity of starch, talc and magnesium stearate was added, carefully mixed and processed into tablets.

CLAIMS

1. A compound of the following formula (I)



(I)

wherein

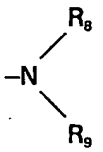
R_1 and R_2 are both hydrogen or R_1 and R_2, taken together, form the group oxo or the group $=CH_2$;

R_3 is a C–6 or C–7 substituent chosen from C_1–C_6 alkyl, C_2–C_5 alkenyl and C_2–C_5 alkynyl;

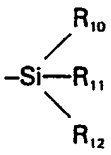
R_4 is a group $-(CH_2)_n-A-Z$, wherein n is zero or an integer of 1 to 3;

A is a bond or represents a C_4–C_7 cycloalkyl ring, a phenyl ring, or a saturated or unsaturated heteromonocyclic ring containing one or more heteroatoms chosen from O, S and N, and

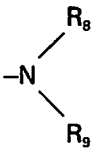
Z is (a) hydrogen, (b) a group



wherein each of R_8 and R_9 is, independently, hydrogen, C_1–C_6 alkyl or phenyl, or R_8 and R_9, taken together with the nitrogen atom to which they are linked, form a saturated heteromonocyclic ring containing one or more heteroatoms chosen from O, S and N; (c) a group



wherein each of R_{10}, R_{11} and R_{12}, which may be the same or different, is C_1–C_6 alkyl or phenyl; (d) a group $-O-(CH_2)_p-R_{13}$, wherein p is zero or an integer of 1 to 5 and R_{13} is hydrogen or a group



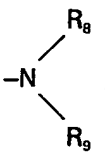
wherein R_8 and R_9 are as defined above; or (e) halogen or a halo-C_1–C_6 alkyl group;

R_5 is C_1–C_6 alkyl;

R_6 is hydroxy and R_7 is hydrogen, C_1–C_6 alkyl, C_2–C_5 alkenyl or C_2–C_5 alkynyl, or R_6 and R_7, taken together, form the group $=CH_2$; and the pharmaceutically or veterinarily acceptable salts thereof.

2. A compound having the formula (I) reported in claim 1, wherein

R_1 and R_2, taken together, form an oxo group; R_3 is C_1–C_6 alkyl; R_4 is a group $-(CH_2)_n-A-Z$ wherein n is an integer of 1 to 3, A is a bond and Z is a group



wherein each of R_8 and R_9 is, independently, hydrogen or C_1–C_6 alkyl; R_5 is C_1–C_2 alkyl; R_6 is hydroxy and R_7 is C_1–C_6 alkyl, C_2–C_5 alkenyl or C_2–C_5 alkynyl; and the pharmaceutically or veterinarily acceptable salts thereof.

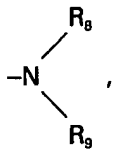
3. A compound selected from the group consisting of:

6β-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(3-N,N-dimethylaminopropyl)-4,5–9,10-estradien-3-one;

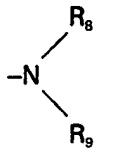
7α-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(3-N,N-dimethylaminopropyl)-4,5–9,10-estradien-3-

one;
6β-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(3-N,N-dimethylaminopropyl)-4,5–9,10-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(3-N,N-dimethylaminopropyl)-4,5–9,10-estradien-3-one;
and the pharmaceutically and veterinarily acceptable salts thereof.

4. A compound having the formula (I) reported in claim 1 wherein R_1 and R_2, taken together, form a group oxo or $=CH_2$; R_3 is C_1–C_6 alkyl; R_4 is a group $-(CH_2)_n-A-Z$, wherein n is zero, A is phenyl and Z is (i)



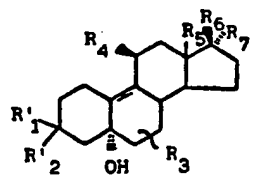
wherein each of R_8 and R_9 is, independently, hydrogen or C_1–C_6 alkyl, or (ii) $-O-(CH_2)_p-R_{13}$ wherein p is 1 or 2 and R_{13} is hydrogen or a group



wherein R_8 and R_9 are as defined above, or (iii) halogen or a halo-C_1–C_6-alkyl group; R_5 is C_1–C_2 alkyl; R_6 is hydroxy and R_7 is C_1–C_6 alkyl, C_2–C_5 alkenyl or C_2–C_5 alkynyl; and the pharmaceutically and veterinarily acceptable salts thereof.

5. A compound selected from the group consisting of:
6β-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylamino-phenyl)-4,5–9,10-estradien-3-one;
6β-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-trifluoromethylphenyl)-4,5–9,10-estradien-3-one;
6β-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-N,N-dimethylaminoethoxyphenyl)-4,5–9,10-estradien-3-one;
7α-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradien-3-one;
7α-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-trifluoromethylphenyl)-4,5–9,10-estradien-3-one;
7α-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-N,N-dimethylaminoethoxyphenyl)-4,5–9,10-estradien-3-one;
6β-methyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-methoxyphenyl)-4,5–9,10-estradien-3-one;
6β-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradien-3-one;
6β-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-trifluoromethylphenyl)-4,5–9,10-estradien-3-one;
6β-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-N,N-dimethylaminoethoxyphenyl)-4,5–9,10-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-trifluoromethylphenyl)-4,5–9,10-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-N,N-dimethylaminoethoxyphenyl)-4,5–9,10-estradien-3-one;
7α-ethyl-17β-hydroxy-17α-(1-propynyl)-11β-(4-methoxyphenyl)-4,5–9,10-estradien-3-one;
6β-methyl-3-methylene-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradiene;
7α-methyl-3-methylene-17β-hydroxy-17α-(1-propynyl)-11β-(4-dimethylaminophenyl)-4,5–9,10-estradiene;
and, where appropriate, the pharmaceutically or veterinarily acceptable salts thereof.

6. A process for the preparation of a compound of formula (I), according to claim 1, or a pharmaceutically or veterinarily acceptable salt thereof, the process comprising dehydrating a compound of formula (II)



(II)

wherein
R_3, R_4, R_5, R_6 and R_7 are as defined in claim 1, R'_1 and R'_2 are both hydrogen or, taken together, form a protected oxo group, or the group $=CH_2$, and if desired, converting a com-

compound of formula (I) into a pharmaceutically or veterinarily acceptable salt thereof or obtaining a free compound from a salt, and/or, if desired, separating a mixture of isomers of formula (I) into the single isomers.

7. A pharmaceutical or veterinary composition containing a suitable carrier and/or diluent and, as an active principle, a compound of formula (I) according to claim 1 or a pharmaceutically or veterinarily acceptable salt thereof.

8. A compound of formula (I) according to claim 1 or a pharmaceutically or veterinarily acceptable salt thereof for use as antiprogesterone or antiglucocorticoid agent.

9. A compound of formula (I) according to claim 1 or a pharmaceutically or veterinarily acceptable salt thereof for use in the treatment of hormone-dependent tumors.

10. A pharmaceutical or veterinary composition according to claim 7 for use as antiprogesterone or antiglucocorticoid agent.

11. A pharmaceutical or veterinary composition according to claim 7 for use in the treatment of hormone-dependent tumors.

12. The use of a compound of formula (I) according to claim 1 or a pharmaceutically or veterinarily acceptable salt thereof in the preparation of a pharmaceutical or veterinary composition for use as antiprogesterone or antiglucocorticoid agent.

13. The use of a compound of formula (I) according to claim 1 or a pharmaceutically or veterinarily acceptable salt thereof in the preparation of a pharmaceutical or veterinary composition for use in the treatment of hormone-dependent tumors.

14. A compound of formula (I) according to claim 1, or a pharmaceutically or veterinarily acceptable salt thereof, hereinbefore specified other than a compound of salt claimed in claim 3 or 5.

15. A process for the preparation of a compound of formula (I) as defined in claim 1 or a pharmaceutically or veterinarily acceptable salt thereof, said process being substantially as hereinbefore described in any one of Examples 10 to 13.

16. A pharmaceutical or veterinary composition substantially as hereinbefore described in Example 14.

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